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Improvement of sympathetic response to exercise by oral administration of ascorbic acid in patients after myocardial infarction

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Abstract

Background: Recent studies indicated that excessive oxidative stress in an animal heart failure model injures both the sympathetic nerve endings and receptors, resulting in disturbance of norepinephrine release and sensitivity to norepinephrine. However, it has not been clarified whether this phenomenon is expressed clinically in patients with heart disease. Therefore, we examined the efficacy of ascorbic acid administration as an antioxidant vitamin in relation to the heart rate and norepinephrine response to exercise in patients after myocardial infarction.

Methods: In this randomized crossover trial, 21 male patients who had had myocardial infarction underwent symptom-limited ergometer cardiopulmonary exercise testing twice, that is, without and with ascorbic acid (2 g) administration. Plasma norepinephrine concentrations were assessed at rest and at peak exercise, and heart rate responsiveness to the norepinephrine increment from rest to peak exercise (ΔHR/logΔNE) was calculated.

Results: In the exercise test after ascorbic acid administration, peak oxygen consumption (VO_2) improved over baseline. Ascorbic acid administration significantly increased the change in heart rate and norepinephrine from rest to peak exercise and ΔHR/logΔNE. The increment in heart rate was significantly correlated with peak VO_2 in each test.

Conclusion: Ascorbic acid intake before exercise improved exercise capacity through enhancement of the heart rate and norepinephrine response to exercise in patients after myocardial infarction. These findings suggest that ascorbic acid intake improves sympathetic dysfunction resulting from injury by excessive oxidative stress after myocardial infarction.

Keywords: Ascorbic acid; Exercise; Norepinephrine; Heart rate; Oxidative stress

1. Introduction

Recent evidence suggests that an increment in oxidative stress aggravates the pathogenetic processes in heart failure [1,2] and in coronary artery disease [3]. Injurious events such as endothelial dysfunction, which result from excessive oxygen free radical species [2–5], play an important role in poor morbidity and mortality. Similarly, some oxidized products have harmful effects in patients with heart diseases [6]. Thus, the direct and/or indirect influences of oxidative stress on the status of heart disease are clinically important. For these reasons, antioxidant therapies for oxidative stress in heart disease have been tried. Results of animal studies demonstrated the efficacy of antioxidant treatment in myocardial infarction [7,8] and heart failure models [9,10]. However, from clinical studies [11,12], it is still controversial whether antioxidants improve the prognosis in chronic cardiovascular disease. Because of this discrepancy between animal and clinical studies in the efficacy of antioxidant therapy, further clinical trials are needed.

The purpose of this present study was to clarify the clinical implications of antioxidant therapy for heart disease. We focused on injury of the sympathetic nervous system via oxidative stress in heart disease because this important matter has not been clarified clinically. Studies

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using an animal model of congestive heart failure showed that the cardiac noradrenergic nerve terminal was impaired via oxidative stress [13] and that antioxidants prevented the development of sympathetic abnormalities resulting from oxidative stress [5]. It could be expected that similar events would take place in humans, but this has not been demonstrated through clinical studies. Sympathetic dysfunction is not rare in patients with heart disease [14,15]. Patients with heart failure frequently have impaired norepinephrine secretion and an attenuated heart rate response to norepinephrine during exercise [16–19], factors that limit exercise capacity. Furthermore, sympathetic impairment in heart disease is reported to be related to a poor prognosis [20]. Thus, alterations in the sympathetic system have important roles in the pathogenesis of heart disease.

The beneficial effect of antioxidants, especially on sympathetic dysfunction, remains clinically unclear. Therefore, in the present study we hypothesized that antioxidant administration in patients after myocardial infarction improves the sympathetic dysfunction resulting from injury by excessive oxidative stress and increases exercise capacity. We utilized ascorbic acid as a safe and well-known water-soluble antioxidant [21]. To test this hypothesis, we designed a crossover trial involving cardiopulmonary exercise tests both with and without administration of ascorbic acid in each study patient after myocardial infarction.

2. Methods

2.1. Study population

Twenty-one male patients were studied more than one month after the onset of myocardial infarction. Those with residual ischemia after the onset had undergone successful percutaneous coronary intervention. Patients with angina pectoris, uncontrolled congestive heart failure or severe renal dysfunction (serum creatinine >3.0 mg/dl) were excluded. Written informed consent for participation in this study was obtained from all subjects in accordance with the ethics committee of our institution. Medications were not changed during this study period. Medical therapy consisted of beta-blocker ($n=13$) and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker ($n=20$).

2.2. Exercise test

All subjects underwent symptom-limited cardiopulmonary exercise tests both without ascorbic acid intake and at 2 h after oral administration of 2 g ascorbic acid, respectively, based on the randomized crossover method. The interval between the two tests was 7 days. We compared results of exercise testing without ascorbic acid with those after ascorbic acid administration.

Symptom-limited cardiopulmonary exercise testing was performed with a cycle ergometer (StrenghErgo.240, Mitsubishi Co., Tokyo, Japan) in a sitting position. After a 4-min rest period, exercise began with a 4-min warm-up at 10 W and 60 rpm, after which intensity was increased incrementally by 1 W every 6 s according to the ramp protocol. Heart rate and 12-lead electrocardiogram were monitored continuously (ML-5000, Fukuda Denshi, Tokyo, Japan). During tests, blood pressure was measured every minute by an automatic indirect cuff monometer (STBD-780B, Nihon Collin Co., Ltd., Aichi, Japan).

Exercise was stopped upon symptoms of exhaustion. No patient experienced angina, syncope, ischemic ST segment changes or serious arrhythmia during exercise. Oxygen consumption (VO_2), carbon dioxide production (VCO_2) and ventilatory equivalent (VE) were measured using a breath-by-breath gas analyzer (AE-300, Minato Medical Science, Osaka, Japan).

2.3. Administration of ascorbic acid

It was reported that 2 g of ascorbic acid produced a significant increment in plasma concentration within the physiological range, and that plasma ascorbic acid reached a plateau after 2 h and remained elevated 5 h after the investigation [22]. In the present study, therefore, we chose the dose of ascorbic acid and timing of exercise testing after administration based on those findings. The ascorbic acid (Iwaki Pharmaceutical Co., Tokyo, Japan) was given orally with sufficient water while the patient was in a fasting state. No subject experienced side effects such as heartburn.

2.4. Measurement of ascorbic acid and norepinephrine concentration

We collected blood samples from the antecubital vein into two tubes while the patient was at rest and at peak exercise. One tube contained oxalic acid for measurement of ascorbic acid and the other contained EDTA for measurement of norepinephrine.

Serum concentration of ascorbic acid was assessed before each exercise test. Ascorbic acid concentration was determined by high-performance liquid chromatography with electrochemical detection using established methodology [23]. Blood samples in the tube containing EDTA were centrifuged at 3000 rpm for 10 min and plasma was extracted. Plasma concentration of norepinephrine was analyzed by high-performance liquid chromatography.

2.5. Assessment of sympathetic function

We examined sympathetic function at rest and during exercise using the response of norepinephrine to exercise and the sinoatrial nodal responsiveness to increments of norepinephrine. The index of sympathetic responsiveness was evaluated by the ratio of the increment in heart rate to